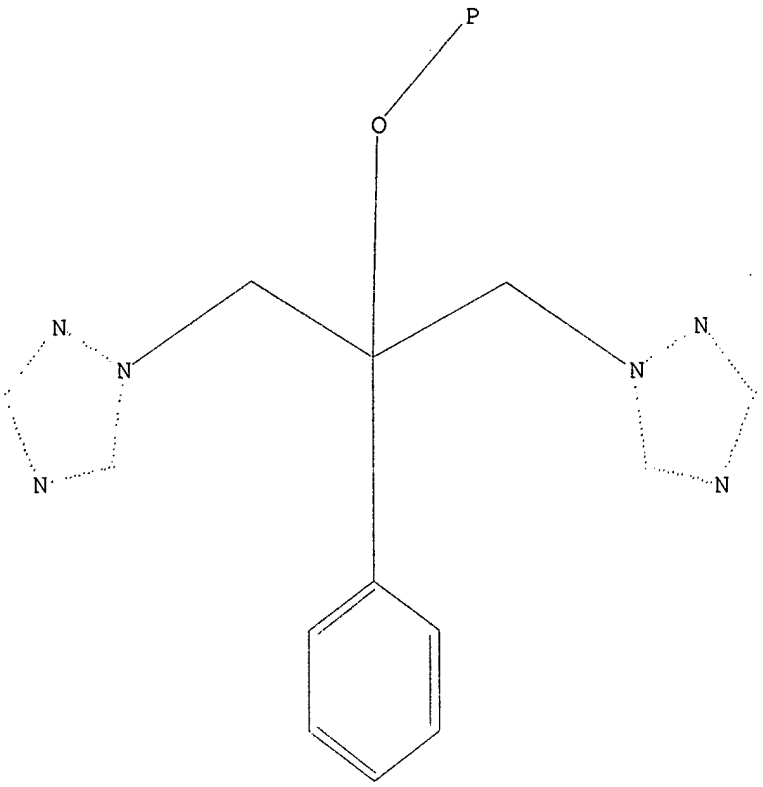

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 17:48:04 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        1 TO ITERATE

100.0% PROCESSED         1 ITERATIONS                                 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO       80
PROJECTED ANSWERS:               1 TO       80

L2            1 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 17:48:07 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       31 TO ITERATE

100.0% PROCESSED        31 ITERATIONS                                21 ANSWERS
SEARCH TIME: 00.00.01

L3           21 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   166.94     167.15

FILE 'CAPLUS' ENTERED AT 17:48:10 ON 03 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 3 Mar 2006 VOL 144 ISS 11
FILE LAST UPDATED: 2 Mar 2006 (20060302/ED)

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=> s l3
L4 14 L3

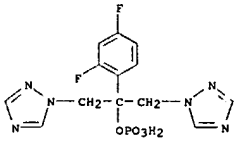
=> d ibib abs hitstr tot

L4 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:532766 CAPLUS
DOCUMENT NUMBER: 143:378787
TITLE: Fosfluconazole (prodif intravenous solution), a therapeutic drug for deep-seated mycosis, that allows reduction in volume load, bolus injection: basic and clinical aspects
AUTHOR(S): Fujiwara, Toyohiro
CORPORATE SOURCE: Dep. of Pharmacy, Suita City Hospital, Japan
SOURCE: Japanese Pharmacology & Therapeutics (2005), 33(4), 267-302
CODEN: JPTABU
PUBLISHER: Raifu Saiensu Shuppan K.K.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review. Fosfluconazole is a prodrug of fluconazole, an azole antifungal agent used worldwide as a therapeutic drug for deep-seated mycosis, It was created at the Central Research Laboratory of Pfizer Ltd. in England by esterification of the hydroxyl group of fluconazole with phosphoric acid. Fosfluconazole is rapidly hydrolyzed to fluconazole by an alkaline phosphatase (Al-P) ubiquitous in the body, and behaves as fluconazole in the body thereby exhibiting clin. effects equivalent to those of fluconazole. Phosphate esterification of fluconazole has endowed the compound with high solubility in aqueous solution of pH 4 to 12. A volume of 200 mL used to be necessary for administering 400 mg fluconazole, whereas as little as 5 mL of solution is needed to administer 400 mg fluconazole-equivalent of fosfluconazole, a 40-fold reduction in the volume, permitting bolus injection. In patients with deep-seated mycosis requiring high dose antifungal agents, multiple concomitant medication as well as adjuvant therapy such as fluid replacement is performed. However, in patients complicated by serious underlying disease, particularly cardiac failure, respiratory failure or ascites, fluid replacement may be restricted to adjust the balance of water content and electrolytes in the body. Compared with fluconazole, fosfluconazole is easier to use in patients with deep-seated mycosis because it can be administered by bolus injection resulting in a marked decrease in volume load. Also, fluconazole had a long elimination half-life (.apprx.30 h), requiring 6 to 10 days for the blood concentration to reach the steady state. In contrast, administration of fosfluconazole using a loading dose method, i.e, a double maintenance dose on the first day and on day 2 followed by the maintenance dose from day 3, allows the plasma fluconazole concentration to be maintained at the steady state level from day 3 onward, enabling the drug to rapidly reach the effective concentration thereby exhibiting the effect. Furthermore, fosfluconazole is indicated for mycotic peritonitis for the first time among deep-seated mycosis agents, in addition to the following diseases for which fluconazole is indicated: fungemia, respiratory tract mycosis, digestive tract mycosis, urinary tract mycosis, and mycotic meningitis.

IT **194798-83-9**, Fosfluconazole
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

L4 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fosfluconazole (prodif i.v. soln.), a therapeutic drug for deep-seated mycosis, that allows redn. in vol. load, bolus injection: basic and clin. aspects)
RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

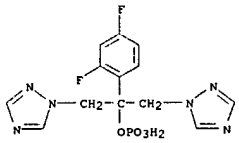


L4 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:217323 CAPLUS
DOCUMENT NUMBER: 143:275
TITLE: The effects of hepatic impairment on the pharmacokinetics of fosfluconazole and fluconazole following a single intravenous bolus injection of fosfluconazole
AUTHOR(S): Sobue, Satoshi; Tan, Keith; Haug-Pihale, Gertraud
CORPORATE SOURCE: Clinical Pharmacology, Pfizer Global R&D, Tokyo Laboratories, Pfizer Japan Inc., Tokyo, Japan
SOURCE: British Journal of Clinical Pharmacology (2005), 59(2), 160-166
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fosfluconazole is a phosphate pro-drug of fluconazole (FLCZ). This study was conducted to determine the pharmacokinetics of fosfluconazole and FLCZ following a single i.v. injection of fosfluconazole in subjects with hepatic impairment and to compare them with healthy subjects. Twenty-four subjects (12 with normal hepatic function and 12 with chronic stable mild to moderate impaired hepatic function) received a single 1000-mg bolus i.v. injection of fosfluconazole. Concns. of fosfluconazole and FLCZ were determined in plasma and urine samples taken up to 192 h and 48 h postdose, resp. The total clearance of fosfluconazole was higher and the t1/2,z and mean residence time were shorter in hepatically impaired subjects than in normal subjects. This may reflect more rapid conversion to FLCZ. The degree of protein binding of fosfluconazole (> 90%) and the amount of fosfluconazole excreted in the urine were similar in both groups. Slightly higher mean plasma concns. of FLCZ were observed in the impaired group than in the normal group; however, hepatic impairment had no statistically significant effect on the FLCZ pharmacokinetic parameters apart from tmax. The tmax values were 4.8 h and 3.1 h in the normal and impaired subjects, resp. The shorter tmax for FLCZ is also consistent with the more rapid conversion in the impaired subjects. The ratios (95% confidence intervals) for Cmax and AUC of FLCZ (impaired/normal) were 106.0% (92.8, 121.2) and 115.6% (86.4, 154.7), resp. There were no serious adverse events, and no discontinuations due to adverse events or laboratory test abnormalities. The adverse events reported were mostly mild in severity and no trend could be discerned between the groups. Fosfluconazole was more rapidly converted to FLCZ in the hepatically impaired subjects but the FLCZ pharmacokinetic parameters (except tmax) were not statistically significantly affected by hepatic impairment. Fosfluconazole was well tolerated by both groups. These results suggest that there is no requirement to adjust the dose of fosfluconazole when administered to subjects with mild to moderate hepatic impairment.

IT **194798-83-9**, Fosfluconazole
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fosfluconazole CL and total plasma clearance of unbound fosfluconazole was significantly higher but mean t1/2,Z, mean residence time, AUC was lower in hepatic impaired subject)
RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-

L4 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:76219 CAPLUS
DOCUMENT NUMBER: 142:177041
TITLE: Preparation of azole monosaccharide as antifungal agents
INVENTOR(S): Parang, Keykavous; Sardari, Soroush; Nam, Nguyen Hai
PATENT ASSIGNEE(S): The Board of Governors for Higher Education State of Rhode Island and Providence Plantations, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005006860	A2	20050127	WO 2004-US23316	20040719
WO 2005006860	A3	20051103		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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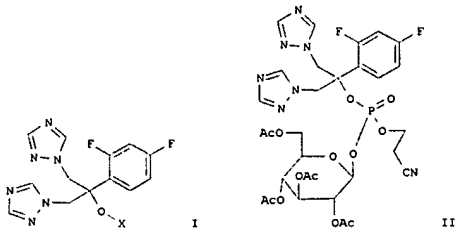
PRIORITY APPLN. INFO.: US 2003-488319P P 20030718
US 2004-543972P P 20040212

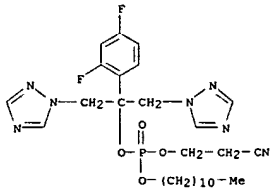
OTHER SOURCE(S): MARPAT 142:177041
GI



AB The present invention is broadly directed to azole derivs. I, wherein X is

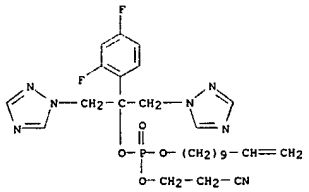
L4 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
COR, P(O)(OR1)(OR2); R is alkyl, aryl, alkene, alkyne, alkyl halide, alkoxy, aryloxy; R1 is H, alkyl, aryl; R2 is alkyl, aryl, alkene, alkyne, alkyl halide, ester substituted six or five member cyclic monosaccharide, that exhibit antifungal activity and methods for making the same. In one aspect, the invention includes carboxylic acid and phosphate ester derivs. of fluconazole that exhibit antifungal activity. In addn., the invention comprises methods for synthesizing the derivs. and pharmaceutical compns. contg. the derivs. Thus, monosaccharide II was prepd. and tested in vitro as antifungal agent.
IT **804566-93-6P 804566-94-7P 804566-95-8P**
804566-96-9P 804566-97-0P 804566-98-1P
804566-99-2P 804567-00-8P
RL: AGR (Agricultural use); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of azole monosaccharide as antifungal agents)

RN 804566-93-6 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl undecyl ester (9CI) (CA INDEX NAME)

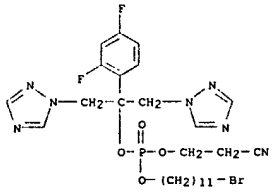


RN 804566-94-7 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl 10-undecenyl ester (9CI) (CA INDEX NAME)

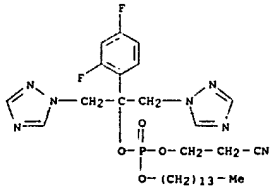
L4 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 804566-95-8 CAPLUS
CN Phosphoric acid, 11-bromoundecyl 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl ester (9CI) (CA INDEX NAME)

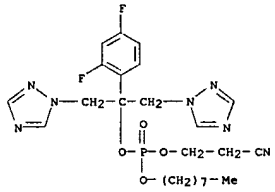


RN 804566-96-9 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl tetradecyl ester (9CI) (CA INDEX NAME)

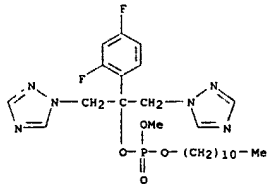


L4 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

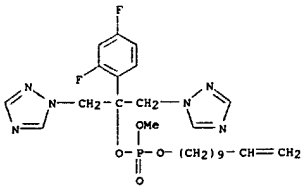
RN 804566-97-0 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl octyl ester (9CI) (CA INDEX NAME)



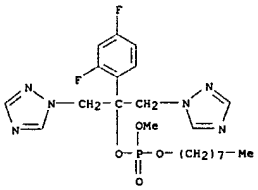
RN 804566-98-1 CAPLUS
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl methyl undecyl ester (9CI) (CA INDEX NAME)



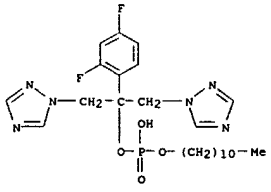
RN 804566-99-2 CAPLUS
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl methyl 10-undecenyl ester (9CI) (CA INDEX NAME)



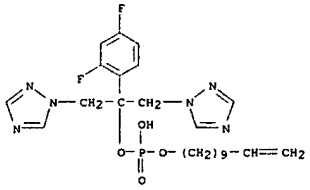
RN 804567-00-8 CAPLUS
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl methyl octyl ester (9CI) (CA INDEX NAME)



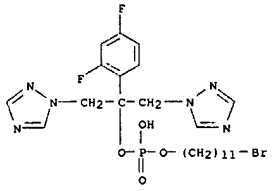
IT **804567-01-9P 804567-02-0P 804567-03-1P**
804567-04-2P 804567-05-3P 804567-06-4P
RL: AGR (Agricultural use); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation);
USES
(Uses)
(preparation of azole monosaccharide as antifungal agents)
RN 804567-01-9 CAPLUS
CN Phosphoric acid, mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] monoundecyl ester (9CI) (CA INDEX NAME)



RN 804567-02-0 CAPLUS
CN Phosphoric acid, mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] mono-10-undecenyl ester (9CI) (CA INDEX NAME)

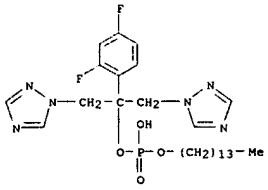


RN 804567-03-1 CAPLUS
CN Phosphoric acid, mono(11-bromoundecyl) mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] ester (9CI) (CA
INDEX NAME)



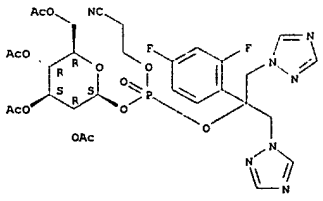
RN 804567-04-2 CAPLUS

CN Phosphoric acid, mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] monotetradecyl ester (9CI) (CA INDEX NAME)



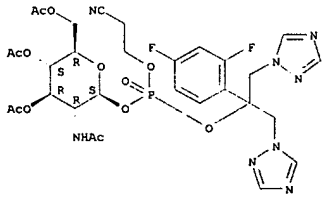
RN 804567-05-3 CAPLUS
CN β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-[2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl phosphate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 804567-06-4 CAPLUS
CN β-D-Glucopyranose, 2-(acetylamino)-2-deoxy-, 3,4,6-triacetate 1-[2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl phosphate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:916843 CAPLUS
DOCUMENT NUMBER: 142:32454
TITLE: Carboxylic acid and phosphate ester derivatives of fluconazole: synthesis and antifungal activities
AUTHOR(S): Nam, Nguyen-Hai; Sardari, Soroush; Selecky, Meredith; Parang, Keykavous
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Bioorganic & Medicinal Chemistry (2004), 12(23), 6255-6269
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:32454

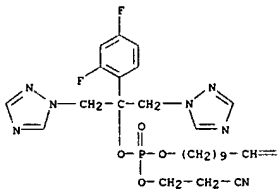
AB Two classes of fluconazole derivs., (a) carboxylic acid esters and (b) fatty alc. and carbohydrate phosphate esters, were synthesized and evaluated in vitro against Cryptococcus neoformans, Candida albicans, and Aspergillus niger. All carboxylic acid ester derivs. of fluconazole, such as O-2-bromooctanoylfluconazole (MIC = 111 μg/mL) and O-11-bromoundecanoylfluconazole (MIC = 198 μg/mL), exhibited higher antifungal activity than fluconazole (MIC ≥ 4444 μg/mL) against C. albicans ATCC 14053 in SDB medium. Several fatty alc. phosphate triester derivs. of fluconazole exhibited enhanced antifungal activities against C. albicans and/or A. niger compared to fluconazole in SDB medium. For example, 2-cyanoethyl-ω-undecylenyl fluconazole phosphate with MIC value of 122 μg/mL had at least 36 times greater antifungal activity than fluconazole against C. albicans in SDB medium. Methyl-undecanyl fluconazole phosphate with a MIC value of 190 μg/mL was at least 3-fold more potent than fluconazole against A. niger ATCC 16404. All compds. had higher estimated lipophilicity and dermal permeability than those for fluconazole. These results demonstrate the potential of these antifungal agents for further development as sustained-release topical antifungal chemotherapeutic agents.

IT **804566-93-6P 804566-94-7P 804566-95-8P 804566-96-9P 804566-97-0P 804566-98-1P 804566-99-2P 804567-00-8P 804567-01-9P 804567-02-0P 804567-03-1P 804567-04-2P 804567-05-3P 804567-06-4P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and antifungal activities of carboxylic acid and phosphate ester derivs. of fluconazole)

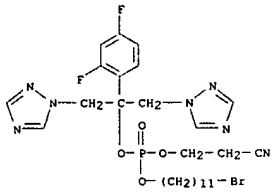
RN 804566-93-6 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl undecyl ester (9CI) (CA INDEX NAME)

L4 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

RN 804566-94-7 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl 10-undecenyl ester (9CI) (CA INDEX NAME)

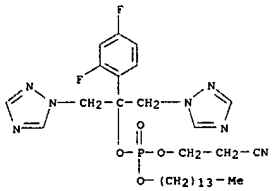


RN 804566-95-8 CAPLUS
CN Phosphoric acid, 11-bromoundecyl 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl ester (9CI) (CA INDEX NAME)

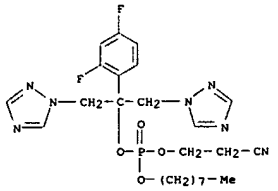


L4 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

RN 804566-96-9 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl tetradecyl ester (9CI) (CA INDEX NAME)

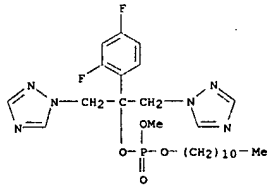


RN 804566-97-0 CAPLUS
CN Phosphoric acid, 2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl octyl ester (9CI) (CA INDEX NAME)

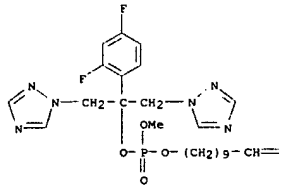


RN 804566-98-1 CAPLUS
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl methyl undecyl ester (9CI) (CA INDEX NAME)

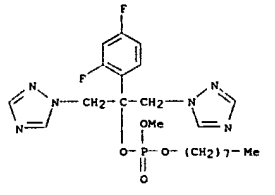
L4 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 804566-99-2 CAPLUS
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl methyl 10-undecenyl ester (9CI) (CA INDEX NAME)

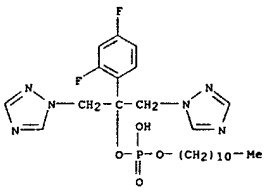


RN 804567-00-8 CAPLUS
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl methyl octyl ester (9CI) (CA INDEX NAME)

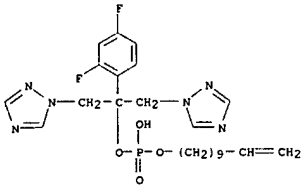


RN 804567-01-9 CAPLUS
CN Phosphoric acid, mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] monoundecyl ester (9CI) (CA INDEX

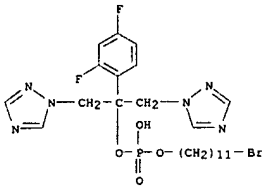
NAME)

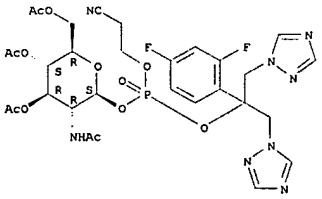


RN 804567-02-0 CAPLUS
CN Phosphoric acid, mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] mono-10-undecenyl ester (9CI) (CA INDEX NAME)



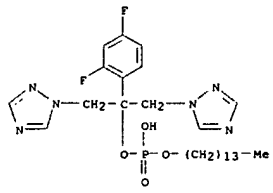
RN 804567-03-1 CAPLUS
CN Phosphoric acid, mono(11-bromoundecyl) mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] ester (9CI) (CA
INDEX NAME)





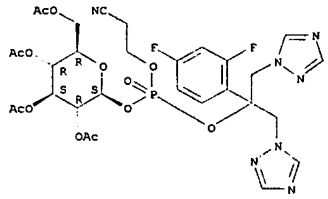
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

RN 804567-04-2 CAPLUS
CN Phosphoric acid, mono[1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl] monotetradecyl ester (9CI) (CA INDEX NAME)



RN 804567-05-3 CAPLUS
CN β-D-Glucopyranose, 2,3,4,6-tetraacetate 1-[2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl phosphate] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 804567-06-4 CAPLUS
CN β-D-Glucopyranose, 2-(acetylamino)-2-deoxy-, 3,4,6-triacetate 1-[2-cyanoethyl 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl phosphate] (9CI) (CA INDEX NAME)

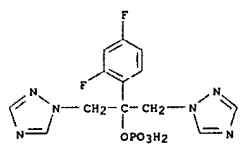
Absolute stereochemistry.

ACCESSION NUMBER:	2004:840408 CAPLUS
DOCUMENT NUMBER:	142:341522
TITLE:	New drugs of the world: 2003
AUTHOR(S):	Murakami, Hisamichi
CORPORATE SOURCE:	Japan
SOURCE:	Fain Kemikaru (2004), 33(10), 49-56 CODEN: FNKMAU; ISSN: 0913-6150
PUBLISHER:	Shi Emu Shi Shuppan
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	Japanese

AB A review on synthetic characteristics and pharmaceutical activities of new
drugs approved in 2003 in Japan and other countries. Drugs covered in this article include bortezomib (Velcade), carglumic acid (Carbaglu), emtricitabine (Emtriva), enfuvirtide (Fuzeon), fosamprenavir calcium (Lexiva), and fosfluconazole (Prodif).

IT **194798-83-9**, Fosfluconazole
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthetic characteristics and pharmaceutical activities of new drugs in 2003)

RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)



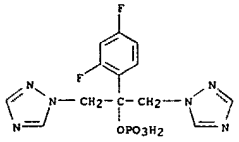
L4 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:635835 CAPLUS
DOCUMENT NUMBER: 142:126499
TITLE: Pharmacokinetics of fosfluconazole and fluconazole following multiple intravenous administration of fosfluconazole in healthy male volunteers
AUTHOR(S): Sobue, Satoshi; Tan, Keith; Layton, Gary; Eve, Malcolm; Sanderson, J. Brian
CORPORATE SOURCE: Clinical Pharmacology, Pfizer Global R & D, Tokyo Laboratories, Pfizer Japan Inc., Tokyo, Japan
SOURCE: British Journal of Clinical Pharmacology (2004), 58(1), 20-25
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aims: To assess the bioavailability of fluconazole (FLCZ) from phosphate prodrug (fosfluconazole), to investigate the effect of loading doses on the time to achieve FLCZ steady state plasma concns. and on safety, and to investigate the pharmacokinetics of fosfluconazole following once daily multiple bolus injection of fosfluconazole in healthy male volunteers. Methods: The first study was a randomized, double-blind, double dummy, two-period crossover study. Subject received either 1000 mg fosfluconazole or 800 mg FLCZ once daily for 14 days in random order. The second study was an open label, randomized parallel group study. Subjects received one of three fosfluconazole once daily treatments: 500 mg for 10 days (no loading dose), a loading dose of 1000 mg on day 1 followed by 500 mg for 9 days (one loading dose), or loading doses of 1000 mg on days 1 and 2 followed by 500 mg for 8 days (two loading doses). Results: The estimated mean (90% CI) bioavailability of FLCZ from fosfluconazole was 96.8% (94.5, 99.2), with a Cmax,ss ratio of 98.3% (93.3, 103.5) in the first study. Less than 1% of the administered dose of fosfluconazole was excreted unchanged in the urine and the majority (85.6%) was eliminated in the urine as FLCZ. In the second study two loading doses regimen led to earlier achievement of target steady state plasma concns. (by day 3) compared with use of one or no loading dose (towards the end of the dosing period). Similar adverse event profiles were seen in all three treatment groups. Fosfluconazole did not accumulate after multiple dosing. Conclusions: Multiple administration of 1000 mg fosfluconazole and 800 mg FLCZ produced equivalent systemic exposure to FLCZ. Steady state FLCZ plasma concns. were achieved earliest when two loading doses were used.

IT **194798-83-9**, Fosfluconazole
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(multiple i.v. administration of 1000 mg fosfluconazole and 800 mg FLCZ produced equivalent systemic exposure to FLCZ and steady state FLCZ plasma concns. were achieved earliest when two loading doses were used in healthy human)

RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

L4 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

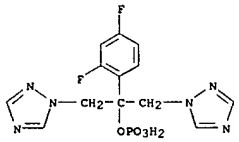
L4 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:560128 CAPLUS
DOCUMENT NUMBER: 141:150515
TITLE: The effects of renal impairment on the pharmacokinetics and safety of fosfluconazole and fluconazole following a single intravenous bolus injection of fosfluconazole
AUTHOR(S): Sobue, Satoshi; Tan, Keith; Layton, Gary; Leclerc, Violette; Weil, Angelika
CORPORATE SOURCE: Clinical Pharmacology, Pfizer Global R+D, Tokyo Laboratories, Pfizer Japan Inc., Tokyo, Japan
SOURCE: British Journal of Clinical Pharmacology (2004), 57(6), 773-784
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fosfluconazole is a phosphate prodrug of fluconazole (FLCZ). This study was conducted to investigate the effect of renal impairment on the pharmacokinetics of fosfluconazole and FLCZ, and to assess the safety and toleration of fosfluconazole following a single i.v. bolus injection of fosfluconazole in subjects with normal and impaired renal function. In an open, parallel-group, two-center study, subjects with normal and impaired renal function received a single 1000-mg bolus i.v. injection of fosfluconazole. Subjects were categorized as Normal (> 80 mL min-1), Mild (51-80 mL min-1), Moderate (30-50 mL min-1) or Severe (< 30 mL min-1) impairment group according to their Cockcroft and Gault creatinine clearance (CLcr) values. Concns. of fosfluconazole and FLCZ were determined in plasma and urine samples taken up to 240 h and 48 h postdose, resp. Fosfluconazole plasma concns. were very similar across the four groups, and there was no apparent relationship between any of the fosfluconazole pharmacokinetic parameters with increasing renal impairment. The conversion of fosfluconazole to FLCZ was unaffected by the degree of renal impairment. Only small amts. of fosfluconazole were excreted in the urine suggesting almost complete conversion to FLCZ. FLCZ concns. were still detected in plasma after 240 h postdose and remained higher at the later sampling times in subjects in the Moderate and Severe groups. The area under the plasma concentration vs. time curve between time zero and infinity (AUC), the terminal elimination phase half-life (t1/2) and the mean residence time (MRT) of FLCZ all increased with the degree of renal impairment. The ratios (95% confidence interval) for AUC (Renal impairment group/Normal group) were 112.8% (89.5, 142.1), 240.6% (128.2, 451.4) and 355.1% (259.3, 486.3) for the Mild, Moderate and Severe impairment groups, resp. There was a linear relationship between CLcr with AUC, t1/2, MRT and the total plasma clearance of FLCZ (CL/F). Both the amount excreted over 48 h in the urine and the renal clearance of FLCZ decreased with an increase in renal impairment. The adverse events reported were mild to moderate in intensity, and there was no observed relationship with impairment group. There were no severe or serious adverse events, and in general fosfluconazole was well tolerated.

IT **194798-83-9**, Fosfluconazole
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

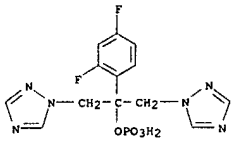
L4 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
(effect of renal impairment on the pharmacokinetics and safety of fosfluconazole and fluconazole)

RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)



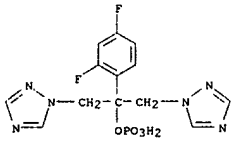
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:543525 CAPLUS
DOCUMENT NUMBER: 141:218070
TITLE: Nonclinical studies and clinical studies on fosfluconazole, a triazole antifungal agent
AUTHOR(S): Kawakami, Yutaka; Nagino, Kenji; Shinkai, Keisuke; Sobue, Satoshi; Abe, Masaaki; Ishiko, Junichi
CORPORATE SOURCE: Pfizer Global R & D, Tokyo Lab., Pfizer Japan Inc., Tokyo, 151-8589, Japan
SOURCE: Nippon Yakurigaku Zasshi (2004), 124(1), 41-51
CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER: Nippon Yakuri Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. Fosfluconazole is a phosphate prodrug of fluconazole that has been developed to reduce the volume of fluid required to administer fluconazole by the i.v. route. Fosfluconazole is hydrolyzed by alkaline phosphatase to fluconazole and phosphoric acid. Fosfluconazole had no significant antifungal activity in vitro. However, in rat models of acute systemic candidiasis and intracranial cryptococcosis, fosfluconazole retained the antifungal potency and efficacy of fluconazole. This reflects the effective conversion of the prodrug to the parent during the course of the expts. The 2-day-loading dose regimen led to earlier achievement of target fluconazole steady state plasma concns. compared to use of the 1-day- or no-loading dose regimen of fosfluconazole. The efficacy and safety of fosfluconazole were investigated with the 2-day-loading dose regimen in patients with deep-seated mycosis caused by Candida and Cryptococcus species. The efficacy rates were 73.8% in the domestic Phase III study and 91.7% in the foreign Phase III study. Adverse events were observed in 31 cases (19.4%) out of 160 in both studies. These results indicate that fosfluconazole is effective for the treatment of deep-seated mycosis and shows no clin. significant adverse events in the Phase III studies.
IT **194798-83-9**, Fosfluconazole
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Prodif; effect of fosfluconazole, triazole antifungal agent)
RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)



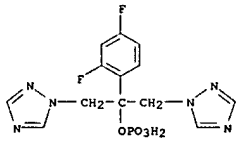
L4 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:506556 CAPLUS
DOCUMENT NUMBER: 142:16192
TITLE: Comparison of the pharmacokinetics of fosfluconazole and fluconazole after single intravenous administration of fosfluconazole in healthy Japanese and Caucasian volunteers
AUTHOR(S): Sobue, Satoshi; Tan, Keith; Shaw, Linda; Layton, Gary; Hust, Rita
CORPORATE SOURCE: Clinical Pharmacology, Pfizer Global R&D, Tokyo Laboratories, Pfizer Japan Inc., Shinjuku Bunka Quint Building 3-22-7, Yoyogi, Shibuya-ku, Tokyo, 151-8589, Japan
SOURCE: European Journal of Clinical Pharmacology (2004), 60(4), 247-253
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The bioavailability of fluconazole (FLCZ) from fosfluconazole (phosphate prodrug of FLCZ) and the comparative pharmacokinetics of fosfluconazole and FLCZ were investigated in Japanese and Caucasian subjects. In a randomized, double-blind, double-dummy, single-dose, two-period, crossover study, 12 Japanese and 12 Caucasian healthy subjects received a bolus i.v. injection of 1000 mg fosfluconazole or an i.v. infusion of 800 mg FLCZ in random order. Concns. of fosfluconazole and FLCZ were determined in plasma and urine samples taken up to 144 h and 48 h post-dose, resp. The bioavailability of FLCZ after administration of fosfluconazole was 95.2% (95% confidence interval: 89.0, 102.0) in Japanese subjects and 100.6% (94.0, 107.7) in Caucasian subjects. The ratio of bioavailabilities (Japanese/Caucasian) was 94.7% (86.0, 104.3). There were no statistically significant differences in the pharmacokinetic parameters of fosfluconazole (except for AUCinf) and FLCZ between Japanese and Caucasian subjects. Although mean AUCinf of fosfluconazole was 25.6% (5.6, 49.2) greater in Japanese subjects, the lack of a statistically significant difference in weight-adjusted CL of fosfluconazole demonstrates that the difference in AUCinf was due to a difference in body weight The adverse-event profile was similar in Japanese and Caucasian subjects after both fosfluconazole and FLCZ dosing, and both treatments were well tolerated in each group. The pharmacokinetics of fosfluconazole and FLCZ were similar in Japanese and Caucasian subjects. Fosfluconazole is almost completely converted to FLCZ and similar systemic exposure to FLCZ is achieved after single doses of fosfluconazole in both Japanese and Caucasian subjects.
IT **194798-83-9**, Fosfluconazole
RL: ADV (Adverse effect, including toxicity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of fosfluconazole conversion to fluconazole in Caucasians and Japanese subjects)
RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

L4 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:260569 CAPLUS
DOCUMENT NUMBER: 141:81400
TITLE: Fosfluconazole
AUTHOR(S): Aikawa, Naoki
CORPORATE SOURCE: Hosp., Keio Univ., Japan
SOURCE: Rinsho to Yakubutsu Chiryo (2004), 23(3), 271-273
CODEN: RYCHEI; ISSN: 0913-7505
PUBLISHER: Eruzebia, Japan K.K.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 6 refs., on the clin. efficacy and safety of title phosphated prodrug of fluconazole (A), in mycosis by comparing its efficacy with that of A.
IT **194798-83-9**, Fosfluconazole
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. efficacy and safety of fosfluconazole, a phosphated prodrug of fluconazole in mycosis)
RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

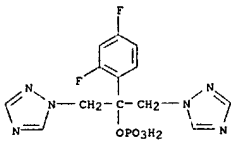


L4 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:255646 CAPLUS
DOCUMENT NUMBER: 141:270938
TITLE: Pharmacokinetics and safety of fosfluconazole after single intravenous bolus injection in healthy male Japanese volunteers
AUTHOR(S): Sobue, Satoshi; Sekiguchi, Kaneo; Shimatani, Katsuyoshi; Tan, Keith
CORPORATE SOURCE: Pfizer Global R+D, Tokyo Laboratories, Pfizer Japan, Inc., Tokyo, Japan
SOURCE: Journal of Clinical Pharmacology (2004), 44(3), 284-292
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This was a single blind, placebo-controlled, escalating single-dose, three-period crossover study using two subject cohorts to investigate the safety, tolerability, and pharmacokinetics in healthy male Japanese subjects after i.v. bolus injection of fosfluconazole 50 to 2000 mg, a phosphate prodrug of fluconazole (FLCZ). Fosfluconazole was rapidly converted to FLCZ with only minor amts. excreted in the urine (less than 4% of the dose). Fosfluconazole had a volume of distribution at the higher doses, which was similar to the extracellular volume in man (0.2 L/kg) and was eliminated with a terminal half-life of 1.5 to 2.5 h. There was apparent dose proportionality in FLCZ pharmacokinetics. Cmax and AUC of FLCZ appeared to increase proportionally with increasing doses of fosfluconazole. There were no apparent dose-dependent trends in tmax, t1/2, or mean residence time (MRT) of FLCZ. Bolus injection of fosfluconazole was well tolerated at doses of up to 2000 mg in healthy Japanese subjects.

IT **194798-83-9**, Fosfluconazole
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(single IV bolus injection of phosphate prodrug of FLCZ, fosfluconazole was safe and well tolerated and there was apparent dose proportionality in FLCZ pharmacokinectics in healthy male japanese volunteer)

RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)



L4 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:39480 CAPLUS
DOCUMENT NUMBER: 140:99592
TITLE: Process for controlling the hydrate mix of a compound
INVENTOR(S): Auffret, Anthony David; Fitzgerald, Michael Paul
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004007689	A1	20040115	US 2003-601355	20030623
CA 2492266	AA	20040122	CA 2003-2492266	20030707
WO 2004007507	A1	20040122	WO 2003-IB3119	20030707
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003247026	A1	20040202	AU 2003-247026	20030707
BR 2003012684	A	20050426	BR 2003-12684	20030707
EP 1534721	A1	20050601	EP 2003-764062	20030707
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005533099	T2	20051104	JP 2004-521009	20030707
PRIORITY APPLN. INFO.:			GB 2002-16515 A	20020716
			US 2002-399491P P	20020729
			WO 2003-IB3119 W	20030707

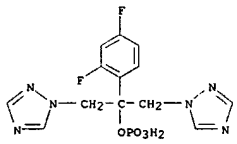
instant app

AB This invention relates to a process for controlling the hydrate mix of a compound, or a composition comprising the compound, the compound being capable of forming a plurality of hydration forms of differing stability and also of dissoln. to give a solution that, when frozen below the eutectic point, is a eutectic mixture This invention further relates to disodium salt of fosfluconazole in the form of its trihydrate, its hexahydrate, or as a mixture of tri- and hexahydrates.

IT **194798-83-9**, Fosfluconazole
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stable hydrate forms of fosfluconazole)

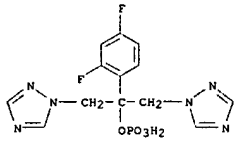
RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

L4 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



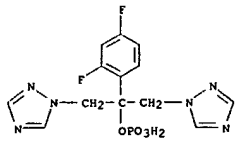
IT **643013-68-7P 643013-69-8P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(stable hydrate forms of fosfluconazole)

RN 643013-68-7 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester), hexahydrate (9CI) (CA INDEX NAME)



●6 H_2O

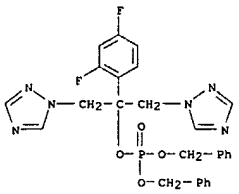
RN 643013-69-8 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester), trihydrate (9CI)
(CA INDEX NAME)



●3 H_2O

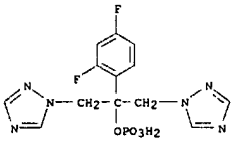
L4 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

L4 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:909509 CAPLUS
DOCUMENT NUMBER: 136:185745
TITLE: The Discovery and Process Development of a Commercial Route to a Water Soluble Prodrug, Fosfluconazole
AUTHOR(S): Bentley, Arthur; Butters, Michael; Green, Stuart P.; Learmonth, William J.; MacRae, Julie A.; Morland, Matthew C.; O'Connor, Garry; Skuse, Joanne
CORPORATE SOURCE: Department of Chemical Research and Development, Pfizer Global Research and Development Laboratories, Kent, CT13 9NJ, UK
SOURCE: Organic Process Research & Development (2002), 6(2), 109-112
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A case history detailing the rationale behind the discovery of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazole-1-yl)-2-Pr dihydrogen phosphate, fosfluconazole (2), a water-soluble prodrug of Diflucan, and the subsequent development of a com. route is presented. Particular items to note are (i) that this compound was discovered in the Chemical Research and Development Department, hence Chemical Research and Development can play a key role in prodrug discovery, (ii) the strategy behind the selection of phosphate ester promoiety, by phosphorylation of a sterically hindered tertiary alc., (iii) the development of the initial route to remove thermally hazardous reagents and to improve processing to allow scale-up, and (iv) the identification and development of the proposed com. process.
IT **194602-25-0P**, Dibenzyl 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazole-1-yl)-2-propyl phosphate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; in manufacture process of water soluble prodrug fosfluconazole)
RN 194602-25-0 CAPLUS
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl bis(phenylmethyl) ester (9CI) (CA INDEX NAME)



IT **194798-83-9P**, Fosfluconazole
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

L4 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
(manuf. process of water sol. prodrug fosfluconazole)
RN 194798-83-9 CAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:533656 CAPLUS
DOCUMENT NUMBER: 127:220800
TITLE: Triazole derivatives useful in therapy
INVENTOR(S): Murtiashaw, Charles W.; Stephenson, Peter T.
PATENT ASSIGNEE(S): Pfizer Research and Development Co., UK; Pfizer Inc.; Murtiashaw, Martha, H.; Green, Stuart; Stephenson, Peter T.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9728169	A1	19970807	WO 1997-EP445	19970127
W: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
TW 434247	B	20010516	TW 1996-85116150	19961227
CA 2240777	AA	19970807	CA 1997-2240777	19970127
CA 2240777	C	20020611		
AU 9715985	A1	19970822	AU 1997-15985	19970127
AU 709781	B2	19990909		
EP 880533	A1	19981202	EP 1997-902288	19970127
EP 880533	B1	20020612		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LV, FI, RO				
JP 10512599	T2	19981202	JP 1997-527312	19970127
JP 2959846	B2	19991006		
CN 1210540	A	19990310	CN 1997-192005	19970127
CN 1085213	B	20020522		
BR 9707257	A	19990406	BR 1997-7257	19970127
RU 2176244	C2	20011127	RU 1998-116435	19970127
IL 124865	A1	20020310	IL 1997-124865	19970127
AT 219089	E	20020615	AT 1997-902288	19970127
PT 880533	T	20020930	PT 1997-902288	19970127
ES 2175336	T3	20021116	ES 1997-902288	19970127
SK 283136	B6	20030304	SK 1998-1022	19970127
CZ 291431	B6	20030312	CZ 1998-2420	19970127
PL 187237	B1	20040630	PL 1997-328436	19970127
ZA 9700826	A	19980731	ZA 1997-826	19970131
HR 970063	B1	20011231	HR 1997-970063	19970131
IL 133135	A1	20030706	IL 1998-133135	19980611
BG 63946	B1	20030731	BG 1998-102603	19980706
NO 9803560	A	19980803	NO 1998-3560	19980803
HK 1018217	A1	20021101	HK 1999-103264	19990729
US 2003144250	A1	20030731	US 2003-339087	20030109
US 6790957	B2	20040914		
US 2004236105	A1	20041125	US 2004-810100	20040326
US 6977302	B2	20051220		
US 2005130940	A1	20050616	US 2005-46266	20050128
PRIORITY APPLN. INFO.:			GB 1996-2080 A	19960202
			IL 1997-124865 A3	19970127
			WO 1997-EP445 W	19970127

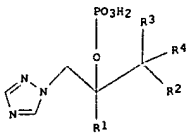
US 1999-117175 B1 19990108

US 2003-339087 A3 20030109

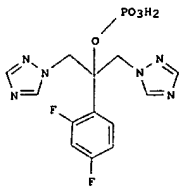
US 2004-810100 A3 20040326

OTHER SOURCE(S): MARPAT 127:220800

GI



I



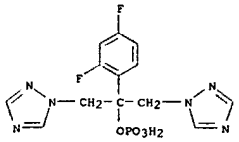
II

AB The preparation of title compds. I (R1 = halo substituted Ph; R2 = 5- or 6-membered nitrogen-containing heterocyclic ring which is optionally substituted by one or more groups selected from halo-, double bond O, substituted Ph; R3 = H, Me; R4 = H; R3R4 = CH2, etc.) or pharmaceutically acceptable salt thereof, useful as fungicide, is described. Thus, phosphorylation of fluconazole with dibenzyl diisopropyl phosphoramidite in the presence of 1H-tetrazole in CH2Cl2 followed by oxidation with 3-chloroperoxybenzoic acid and catalytic debenzylation gave title compound II. The solubility of disodium salt of II was > 150 in comparison to parent compound Aqueous formulation of II for i.v. injection is described. The compds. of the invention are useful in the treatment of fungal infections, and have good aqueous solubility

IT **194798-85-1P 194798-89-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and fungicidal activity of)

RN 194798-85-1 CAPLUS

CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester), disodium salt (9CI) (CA INDEX NAME)



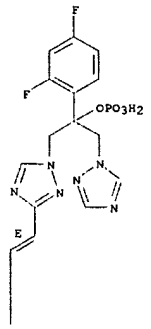
●2 Na

RN 194798-89-5 CAPLUS

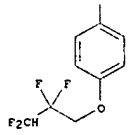
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-3-[2-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]ethenyl]-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester), (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



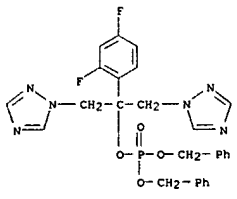
PAGE 2-A



IT **194602-25-0P 194798-95-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of phosphorylated triazole derivs. for treatment of fungal infections)

RN 194602-25-0 CAPLUS

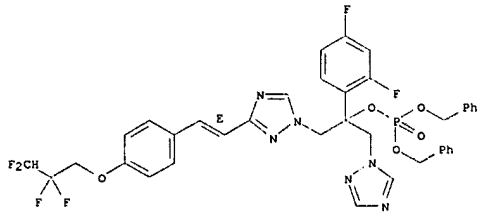
CN Phosphoric acid, 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-1-(1H-1,2,4-triazol-1-ylmethyl)ethyl bis(phenylmethyl) ester (9CI) (CA INDEX NAME)



RN 194798-95-3 CAPLUS

CN Phosphoric acid, 1-(2,4-difluorophenyl)-1-[[3-[2-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]ethenyl]-1H-1,2,4-triazol-1-yl]methyl]-2-(1H-1,2,4-triazol-1-yl)ethyl bis(phenylmethyl) ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **194798-83-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation, salt formation, and fungicidal activity of)

RN 194798-83-9 CAPLUS

CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)